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(54) Method for the preparation of  
arylethylamines

(57) Arylethylamines are obtained by  
electrolytic reduction of the corres-  
ponding aryl nitroethene in the pre-  
sence of a hydroxylamine in the catho-  
lyte using a strong negative cathode  
potential during the entire process.

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## SPECIFICATION

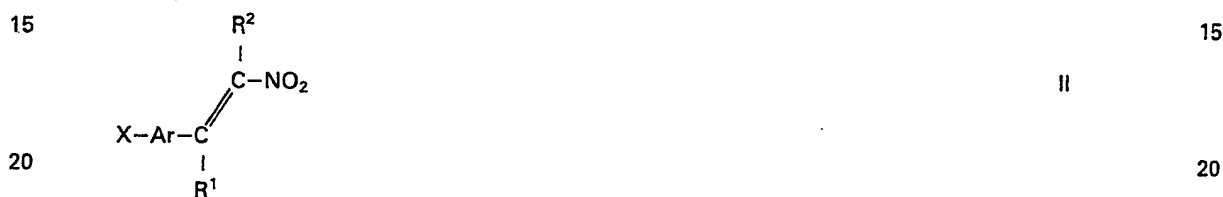
## Method for the preparation of arylethylamines

5 This invention relates to an improved method of electro-chemically reducing 1-aryl-2-nitroethenes to  
arylethylamines. 5

Although the electrochemical reduction of nitrostyrenes has been described in the chemical literature (cf  
for instance Japanese Patent 49-13777), the use of this technique as a practical preparation of  
phenylethylamines has seldom been realised because of insufficient chemical efficiency.

10 It has now been found that a method for preparing arylethylamines in water solutions in high yields and  
with excellent purity can be achieved. 10

This new method is characterized by electrochemical reduction of a 1-aryl-2-nitroethene of the formula



wherein Ar is an aromatic group, X is hydrogen or one or more substituents on the aromatic group selected  
25 from alkyl, alkoxy, hydroxy, 25



35 (R<sup>3</sup> and R<sup>4</sup> are the same or different and each representing hydrogen or alkyl),  $-\text{N}(\text{CH}_2)_n$  (n=4,5,6), 35

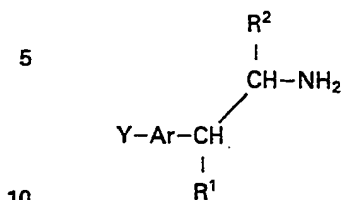


45  $-\text{CN}$ ,  $-\text{COOR}^3$ ,  $-\text{CF}_3$ ,  $-\text{NO}_2$  and halogen, R<sup>1</sup> is hydrogen or methyl and R<sup>2</sup> is hydrogen or an alkyl group with  
1-4 carbon atoms, in the presence of hydroxylamine or a salt thereof and with a strong negative cathod  
potential during the entire process to form an arylethylamine of the formula

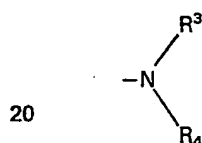


or a pharmaceutically acceptable salt thereof, in which formula Ar, R<sup>1</sup> and R<sup>2</sup> have the meaning given above  
60 and Y is as defined for X with the exception that it does not represent  $-\text{NO}_2$ . 60

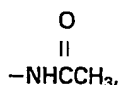
The arylethylamines have the general formula



wherein Ar is an aromatic group, Y is hydrogen or one or more substituents in the aromatic group selected from alkyl, alkoxy, hydroxy,



(R<sup>3</sup> and R<sup>4</sup> are the same or different and each representing hydrogen or alkyl),  $-\text{N}(\text{CH}_2)_n$  (n = 4, 5, 6),



—CN, —COOR<sup>3</sup>, —CF and halogen, R<sup>1</sup> is hydrogen or methyl and R<sup>2</sup> is hydrogen or an alkyl group with 1-4 carbon atoms.

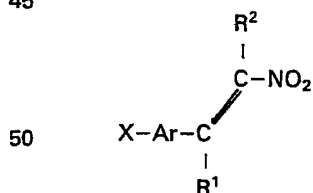
Aromatic groups of interest in this Application are for instance phenyl, naphthyl or indolyl.

Alkyl groups of interest in this Application are straight or branched alkyl groups with 1-5 carbon atoms, for instance methyl, ethyl, n-propyl and isopropyl.

Alkoxy groups of interest in this Application are alkyl-O- groups where the alkyl moiety is defined as above. Halogeno groups of interest in this Application are chloro, bromo and fluoro.

The phenylethylamines of formula I obtained by the method of the invention can be in the form of pharmaceutically acceptable salts e.g. a hydrobromide, hydrochloride, phosphate, sulphate, citrate or tartrate.

The compounds of formula I are useful as pharmaceuticals. The nitroarylethenes used as starting material in the process of this invention have the formula



wherein Ar, R<sup>1</sup> and R<sup>2</sup> have the meaning given above and X is as defined for Y but can also represent —NO<sub>2</sub>.

The catholyte may consist of a dilute aqueous solution of a strong acid alone or a mixture of a strong acid, water and an organic solvent. The strong acid is for example sulfuric, hydrochloric, hydrobromic, phosphoric or a sulfonic acid. The concentration of acid and organic solvent if the later has acid-base properties should be such that the hydronium ion concentration is between 10<sup>-5</sup> M and 20 M, preferably more than 10<sup>-3</sup> M.

The relative amounts of water and organic solvent can be varied over a wide range. The organic solvent may be an alcohol, carboxylic acid, ether, amide or nitrite. The ratio between catholyte volume and cathode area should be as small as possible.

The anolyte may consist of diluted aqueous mineral acids, preferably sulfuric or hydrochloric acid. The concentration is from 2% to 10% by volume.

The anode is normally a DSA®-anode (metal anode overlaid with noble metal oxides) but may also consist

of lead, lead dioxide, graphite or platinum metals.

The cathode material must be carefully chosen. It must have an electrode surface with high hydrogen overpotential. This is achieved by making the cathode of a material with high hydrogen overpotential or by electrodeposition of a metal with high hydrogen overpotential on the cathode before or during the process.

- 5 The cathode material may be zinc, lead, cadmium, mercury, tin, or conducting materials (for example graphite, lead, nickel, copper, aluminium, titanium) on which deposition of for example zinc, lead, cadmium, tin or mercury can be done. 5

The electrolytic cell should be a divided one with good mass transport properties. The diaphragm can be of the ion exchanging type or a plastic tissue.

- 10 The temperature should be as low as possible. The process is usually carried out at temperatures below 20°C. 10

Cathode potential, current density, concentration of nitrostyrene and mass transport properties to the cathode surface are a function of each other. According to the invention it has been found that a large negative potential is important to carry out the reduction successfully. Therefore the reduction should be

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TABLE 1



Run no.	Substrate mols	H <sub>2</sub> O ml	Cosolvent ml	Acid <sup>e)</sup> ml	Catholyte conditions Hydroxyl amm. salt ml	Metal salt mg	pH	Temp. °C	Cathode	Current density A/dm <sup>2</sup>	Potential <sup>e)</sup> VSCE	Amp. hours	Chemical efficiency %
1	0.05	105	-	H <sub>2</sub> SO <sub>4</sub> 6	-	ZNCO <sub>3</sub> 100	0.2	16	Pb	15	-1.55→-2.00	45.8	66
2	"	"	-	"	(NH <sub>2</sub> -OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub> 0.018	"	"	"	"	"	"	"	80
3	"	"	-	"	"	"	"	23	"	35	-1.60→-1.80	"	80
4	"	"	-	"	"	"	"	"	"	"	-1.60→-1.90	49	86
5	0.14	"	-	"	"	"	"	"	"	"	-1.55→-1.90	79	79
6	0.0045	"	-	"	0.018	"	"	16	"	10.8	-1.40→-1.46	42	81
7	0.05	210	-	"	0.036	200	"	23	"	35	-1.72→-1.90	45.5	74
8	0.0045	105	-	"	0.018	100	"	16	Graphite	10.8	-1.65→-1.53	4.2	74
9	"	"	-	"	"	"	"	52	Pb	27.5	-1.40→-1.47	"	72
10	"	95	-	"	"	"	-	16	"	10.8	-1.25→-1.42	"	79
11	"	80	-	"	(NH <sub>2</sub> -OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub> 30	"	-	"	"	"	-1.28→-1.42	4.2	76

TABLE 1 (cont...)

Run no.	Substrate mols	H <sub>2</sub> O ml	Cosolvent ml	Acid <sup>e)</sup> ml	Catholyte conditions			Metal salt mg	pH	Temp. °C	Cathode	Current density A/dm <sup>2</sup>	Potential <sup>e)</sup> VSCE	Amp. hours	Chamic- al efficiency %
					Hydroxyl amm. salt										
12	0.0045	100	-	HCl	5	-		ZnCO <sub>3</sub>	100	0.4	16	Pb	15→12.5 <sup>e)</sup> -1.6 <sup>d)</sup>	4.2	78
							(NH <sub>2</sub> OH) <sub>2</sub>								
13	0.014	17	MeOH 89	H <sub>2</sub> SO <sub>4</sub>	4.1	H <sub>2</sub> SO <sub>4</sub>	0.008	"	"	"	"	"	-	11.1	86
14	"	45	EtOH 60	"	6	"	"	"	"	"	"	"	≈-2.1	"	83
15	"	"	i-PrOH "	"	"	"	"	"	"	"	"	"	-	"	81
16 <sup>b)</sup>	0.032	27	MeOH 87	40% HBr	20	-	a)		-	-	"	13.5	-1.20→-1.70	20.4	61

a) Zinc was electro-deposited on the cathode surface before the nitrostyrene reduction.

b) The conditions according to Japanese Patent 49-13777.

c) The acid volume before the electrolysis.

d) Constant potential electrolysis.

e) The arrows show the changes during the electrolysis.

## Example 2



The same equipment was used and the experiments were run in the same manner as in example 1.

TABLE 2

Run no.	Substrate mols	H <sub>2</sub> O ml	Cosolvent ml	Acid <sup>a)</sup> ml	Catholyte conditions	Hydroxyl amm. salt	Metal salt mg	Temp. °C	Cathode	Current density A/dm <sup>2</sup>	Cathode potential <sup>b)</sup> VSCE	Amp. hours	Chemical efficiency %
1	0.0106	27	MeOH 87	HCl	22	-	ZnO 100	16	Pb	13.5	-1.50→-1.54	15.8	60
2	"	"	"	"	"	(NH <sub>2</sub> OH) H <sub>2</sub> SO <sub>4</sub> 0.012	"	"	"	"	-1.49→-1.55	"	81

a) The acid volume before the electrolysis.

b) The arrows show the changes during the electrolysis.

## Example 3

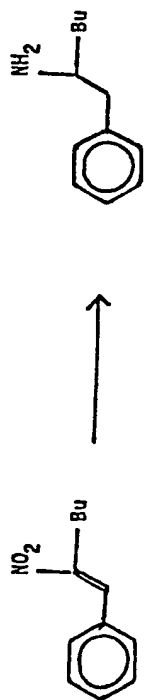


The same equipment was used and the experiments were run in the same manner as in example 1.

TABLE 3

Run No.	Substrate mols	H <sub>2</sub> O Cosolvent ml	Acid <sup>a)</sup>	Hydroxyl/amm. salt	Catholyte conditions	Temp	Cathode	Current density	Cathode potential <sup>b)</sup>	Amp. hours	Chemical efficiency %
			ml	ml	mols	mg °C		A/dm <sup>2</sup>	V/SCE		
1	0.0106	27	MeOH 87	HCl 22	(NH <sub>4</sub> OH) <sub>2</sub> ZnO 0.012	100 16	Pb	13.5	≈ -1.52	27.8	80
					H <sub>2</sub> SO <sub>4</sub>						
2	"	"	"	"	"	"	"	5	-1.0→-1.1	"	57
3	"	"	"	"	-	"	"	13.5	≈ -1.5	"	70

### Example 4

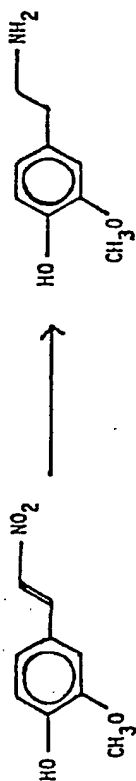


The same equipment was used and the experiment was run in the same manner as in example 1.

TABLE 4

<i>Run no.</i>	<i>Substrate</i>	<i>H<sub>2</sub>O ml</i>	<i>Solvent</i>	<i>Acid<sup>(c)</sup></i>	<i>Catholyte conditions</i>			<i>Temp. °C</i>	<i>Cathode</i>	<i>Current density A/dm<sup>2</sup></i>	<i>Cathode potential V/SCE</i>	<i>Amp. hours</i>	<i>Chemical efficiency %</i>
		<i>ml</i>			<i>Hydroxyl amm. salt</i>		<i>Metal salt</i>	<i>°C</i>					
	<i>mols</i>		<i>ml</i>	<i>ml</i>		<i>mols</i>	<i>mg</i>						
	0.0024	27	MeOH 87	HCl	22	(NH <sub>2</sub> OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub>	ZnO	16	Pb	13.5	-1.32-1.38	27.8	93

## Example 5



The experiment was run as in example 1 except that the anolyte consisted of 90% ethanol and 10% concentrated sulfuric acid.

TABLE 5

Run no.	Substrate	H <sub>2</sub> O		Cosolvent	Acid <sup>a)</sup>	Catholyte conditions		Metal salt	Temp. °C	Cathode	Current density	Cathode potential	Amp. hours	Chemical efficiency %
		ml	ml			Hydroxyl amm. salt	mols				Al/dm <sup>2</sup>	V/SCE		
0.25		15		MeOH	HCl	10	(NH <sub>2</sub> OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub>	0.02	23	Pb	12.5	-1.8-4.0	45	85
				175				ZnSO <sub>4</sub>	300					
				ml				mg						

## Example 6

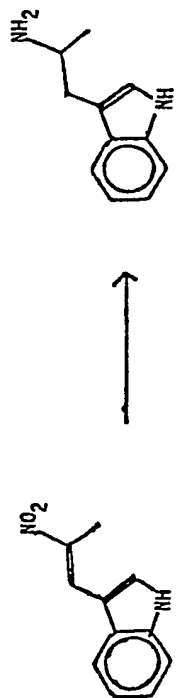


The experiment was run as in Example 5.

TABLE 6

Run no.	Substrate mols	H <sub>2</sub> O ml	Cosolvent ml	Acid <sup>Cl</sup> ml	Catholyte conditions			Temp. °C	Cathode	Current density A/dm <sup>2</sup>	Cathode potential VISCE	Amp. hours	Chemical efficiency %
					Hydroxyl amm. salt ml	amm. salt mols	Metal salt mg						
0.25	15	MeOH 175	HCl	10	(NH <sub>2</sub> OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub>	0.02	ZnSO <sub>4</sub>	300 24	Pb	12.5	-1.8 -4.5	45	85

## Example 7



The same equipment was used and the experiment was run in the same manner as in Example 1.

TABLE 7

Run no	Substrate mols	Solvent		Acid <sup>(c)</sup>	Catholyte conditions		Temp. °C	Cathode	Current density $A/dm^2$	Cathode potential VISCE	Amp. hours	Chemical efficiency %
		H <sub>2</sub> O ml	MeOH ml		Hydroxyl amm. salt ml	Metal salt mols						
0.1	35	MeOH 90	HCl	25	(NH <sub>2</sub> OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub>	0.01	100	Pb	12.5	-2.0 -3.0	10	60

## Example 8



The experiment was run as in Example 1, except that the electrolyte consisted of 60% THF and 40% 1 M H<sub>2</sub>SO<sub>4</sub>.

TABLE 8

Run no.	Substrate mols	H <sub>2</sub> O ml	Cosolvent ml	Acid <sup>d)</sup> ml	Catholyte conditions Hydroxyl amm. salt mls	Metal salt mg	Temp. °C	Cathode	Current density Al/dm <sup>2</sup>	Cathode potential V/SCE	Amp. hours	Chemical efficiency %
	0.005	35	THF 60	H <sub>2</sub> SO <sub>4</sub> 5	(NH <sub>2</sub> OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub> 0.006	ZnCO <sub>3</sub> 36		Pb	10		6.7	80

## Example 9



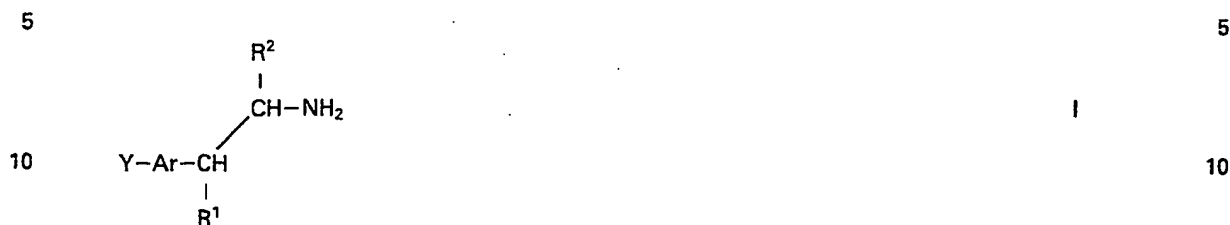
The experiment was run as in Example 8.

TABLE 9

Run no.	Substrate mols	H <sub>2</sub> O ml	Cosolvent ml	Acid <sup>a)</sup> ml	Catholyte conditions			Cathode	Current density Aldm <sup>2</sup>	Cathode potential VISCE	Amp. hours	Chemical efficiency %
					Hydroxyl amm. salt ml	amm. salt mols	Metal/salt mg					
.	.	35	THF 60	H <sub>2</sub> SO <sub>4</sub> 5	(NH <sub>2</sub> OH) <sub>2</sub> H <sub>2</sub> SO <sub>4</sub>	0.006	ZnCO <sub>3</sub> 36	Pb	10	-	4	90

## CLAIMS

1. A method for the preparation of an aryethylamine of the formula



15 or a pharmaceutically acceptable salt thereof, in which formula Ar is an aromatic group, Y is hydrogen or one 15 or more substituents in the aromatic group selected from alkyl, alkoxy, hydroxy,



25 (R<sup>3</sup> and R<sup>4</sup> are the same or different and each representing hydrogen or alkyl, -N(CH<sub>2</sub>)<sub>n</sub> (n = 4,5,6), 25



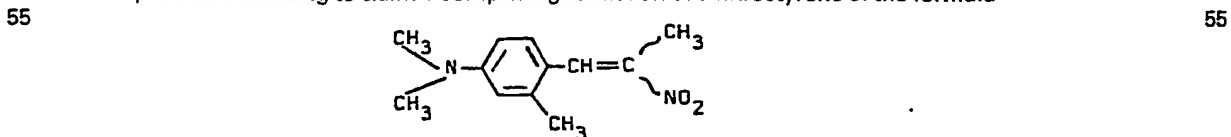
35 -CN, -COOR<sup>3</sup>, -CF<sub>3</sub> and halogen, R<sup>1</sup> is hydrogen or methyl, and R<sup>2</sup> is hydrogen or an alkyl group with 1-4 carbon atoms comprising electrochemical reduction of a nitrostyrene of the formula 35



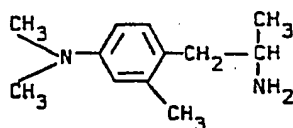
45 wherein Ar, R<sup>1</sup> and R<sup>2</sup> have the meaning given above and X is as defined above for Y but additionally can also represent -NO<sub>2</sub>, in the presence of hydroxylamine or a salt thereof and with a strong negative cathode potential during the entire process.

2. A method according to claim 1 wherein Ar is a benzene, naphthalene or indene residue.  
50 3. A method according to claim 1 or 2 wherein X is dimethylamino, methyl, hydrogen, hydroxy or methoxy.

4. A method according to any one of the preceding claims wherein R<sup>1</sup> is hydrogen.  
5. A method according to any one of the preceding claims wherein R<sup>2</sup> is hydrogen, methyl or butyl.  
6. A process according to claim 1 comprising reduction of a nitrostyrene of the formula



to a phenethylamine of the formula



5

5

7. A method according to any one of the preceding claims wherein the catholyte comprises aqueous acid.
8. A method according to claim 7 wherein the hydronium ion concentration in the catholyte is  $10^{-5}$ M to 20M.
9. A method according to claim 7 or 8 wherein the catholyte comprises an organic solvent.
10. A method according to claim 9 wherein the solvent is methanol, ethanol, isopropanol or tetrahydrofuran.
11. A method according to any one of the preceding claims wherein the catholyte comprises more than 0.1 M hydroxylamine or a salt thereof.
12. A method according to any one of the preceding claims wherein the anolyte comprises 2-10% by volume sulphuric acid or hydrochloric acid.
13. A method according to any one of the preceding claims wherein the cathode is lead.
14. A method according to any one of the preceding claims wherein a negative potential more negative than 1 volt, relative to a standard calomel electrode, is used.
15. A method according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.